Differences Among Major Depressive Disorder With and Without Co-occurring Substance Use Disorders and Substance-Induced Depressive Disorder: Results From the National Epidemiologic Survey on Alcohol and Related Conditions

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ABSTRACT

Objective: To investigate the association between substance use disorders (SUDs) and the clinical presentation, risk factors, and correlates of major depressive disorder (MDD) by examining differences among 3 groups: (1) individuals with lifetime MDD and no comorbid SUD (MDD-NSUD); (2) individuals with comorbid MDD and SUD (MDD-SUD); and (3) individuals with substance-induced depressive disorder (SIDD).

Method: Data were derived from the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions (N = 43,093). Diagnoses were made using the Alcohol Use Disorder and Associated Disabilities Interview Schedule–*DSM-IV* Version.

Results: The lifetime prevalence of MDD-NSUD was 7.41%, whereas those of MDD-SUD and SIDD were 5.82% and 0.26%, respectively. Overall, risk factors for MDD were more common among individuals with MDD-SUD and SIDD than among those with MDD-NSUD. Individuals with MDD-SUD and SIDD had similar rates of comorbidity with any psychiatric disorder, but both groups had higher rates than individuals with MDD-NSUD (odds ratio [OR] = 2.3; 95% CI, 1.9–2.7 and OR = 2.5; 95% CI, 1.4–4.4, respectively). Individuals with SIDD were significantly less likely to receive medication than those with MDD-SUD or MDD-NSUD (OR = 0.5; 95% CI, 0.3–0.9 for both groups).

Conclusions: MDD-SUD is associated with high overall vulnerability to additional psychopathology, a higher number of and more severe depressive episodes, and higher rates of suicide attempts in comparison to individuals with MDD-NSUD. SIDD has low prevalence in the general population but is associated with increased clinical severity and low rates of medication treatment. Similar patterns of comorbidity and risk factors in individuals with SIDD and those with MDD-SUD suggest that the 2 conditions may share underlying etiologic factors.

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High rates of co-occurrence of substance use disorder (SUD) and depressive symptoms have been frequently reported in clinical[1–4] and community samples[5–9] and found to predict poorer mental health, shorter time to relapse of substance use,[10,11] and worse short- and long-term prognosis.[12–17] An important clinical problem is determining which depressive syndromes arising in the context of substance use differ sufficiently from primary major depressive disorder (MDD) to constitute a distinct nosologic entity or require a different treatment approach.

DSM-IV[18] distinguishes between episodes in which the depressive syndrome is primary or independent from the SUD (MDD-SUD) and episodes that appear etiologically linked to the use of substances, ie, substance-induced mood disorder with predominant depressive symptoms (SIDD). In MDD-SUD, the depressive syndrome begins prior to the onset of SUD or occurs during extended abstinence, and the comorbid SUD is not assumed to be causally related to the depressive symptoms. In contrast, SIDD occurs only in the context of substance use and exceeds the expected effects of the particular substances.[18]

The existing literature contains discrepant results, calling into question the validity of the distinction between independent and substance-induced disorders.[19] Some studies have found that individuals with co-occurring MDD and alcohol use disorder (AUD) are more likely than those with SIDD to be female, white, and married[20]; to have attempted suicide[20]; to have an earlier onset of depression and longer depressive episodes[20]; and to have higher rates of family history of mood disorders[21] and less likely to seek treatment for AUD.[21] However, other studies have either failed to find differences between these 2 diagnostic groups in demographic characteristics other than gender and depressive symptoms[22] or found that, if sufficiently long substance-free periods occurred, many depressive episodes originally diagnosed as SIDD were reclassified as MDD.[23,24] Furthermore, the presence of a clinically significant mood syndrome, regardless of its diagnosis as an independent or substance-induced disorder, has adverse prognostic implications for the outcome of SUD.[19,25–27]

Most previous research has focused on individuals with AUD rather than including individuals with other SUD diagnoses[22,28–31] and has relied on treatment-seeking samples,[22,30] which may not extrapolate to more general populations. Furthermore, to date, no study has compared the clinical characteristics, comorbidity patterns, risk factors, or treatment utilization patterns in individuals with SIDD and individuals with MDD-SUD. The goal of this study was to fill these gaps in knowledge by using a nationally representative sample of US adults to examine the characteristics of 3 groups: (1) individuals with lifetime MDD and no comorbid SUD (MDD-NSUD); (2) individuals with MDD-SUD; and (3) individuals with SIDD.

METHOD

The 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) is a survey of a representative sample of the US adult

population (N = 43,093).[7,32] The research protocol received human subjects review and approval from the US Census Bureau and the US Office of Management and Budget. The diagnostic interview used was the Alcohol Use Disorder and Associated Disabilities Interview Schedule–*DSM-IV* Version (AUDADIS-IV).[33]

Lifetime MDD was defined as having at least 1 major depressive episode over the life course without history of manic, mixed, or hypomanic episodes. The *DSM-IV* MDD diagnosis excludes episodes due to substance use, a medical condition, or bereavement.[34] In differentiating substance-induced from independent disorders, AUDADIS used specific questions about the temporal relationship between intoxication or withdrawal and the full depressive syndrome.[35–38] The test-retest reliability and validity of the AUDADIS-IV measure of lifetime MDD are good.[39,40]

SIDD was diagnosed if the full MDD syndrome occurred when the respondent was drinking heavily or more than usual, was using drugs, was experiencing withdrawal, or had ceased alcohol/drug use within the last month. To ensure a stringent test of differences between MDD and SIDD, respondents were classified as having lifetime SIDD if all their depressive episodes were substance-induced and they had no history of MDD. Furthermore, we subdivided the sample of individuals with MDD into those with no lifetime SUD comorbidity (MDD-NSUD) and those with lifetime SUD comorbidity (MDD-SUD). The latter group included 339 individuals who, in addition to lifetime MDD and SUD, reported at least 1 SIDD episode.

Other mood and anxiety disorder diagnoses excluded mental disorders that were substance-induced or due to a medical condition. Test-retest reliabilities of AUDADIS-IV measures of mood and anxiety disorders are fair to good.[39,40]

Consistent with *DSM-IV*, lifetime substance abuse diagnoses required at least 1 of the 4 criteria for abuse either in the 12-month period preceding the interview or previously. Substance dependence diagnoses required at least 3 of the 7 *DSM-IV* criteria for dependence.[38] The test-retest reliabilities of AUDADIS-IV alcohol and drug disorders measures are excellent.[39,41,42]

Personality disorders assessed included avoidant, histrionic, dependent, obsessive-compulsive, paranoid, schizoid, and antisocial personality disorder. The reliability of the AUDADIS-IV diagnoses of personality disorders in community samples is fair to good.[39,43,44]

Other Measures

Age at onset, number of episodes, duration of longest episode, use of alcohol or drugs to help relieve depressive symptoms, treatment utilization, and age at first treatment were ascertained among respondents with lifetime MDD. Consistent with prior research,[45,46] we organized the risk factors into familial influences, risk factors with childhood onset, and risk factors manifested in adulthood. Respondents were classified as receiving treatment if, for depressive symptoms, they ever (1) visited a counselor, therapist, physician, or psychologist; (2) were a patient in a hospital for at least 1 night; (3) visited an emergency room; or (4) were prescribed medications.

Clinical Points

- The combination of major depressive disorder and substance use disorder (MDD-SUD) is common and associated with higher severity and rates of comorbidity than MDD alone.
- Substance-induced depressive disorder (SIDD) has low prevalence and may have similar risk factors and clinical presentation as MDD-SUD.
- Failure to treat depressive symptoms in SIDD may be associated with higher rates of substance use to relieve depressive symptoms.

Statistical Analysis

Weighted percentages and means were computed to derive prevalence, sociodemographic and clinical characteristics, and risk factors of respondents with MDD-NSUD, MDD-SUD, and SIDD. Logistic regression analyses yielded odds ratios (ORs) that indicate measures of association between MDD-NSUD, MDD-SUD, and SIDD and lifetime comorbid psychiatric disorders, MDD risk factors, clinical characteristics, and rates of treatment-seeking. These associations were further adjusted for the sociodemographic characteristics of the sample separately. All analyses were conducted with SUDAAN.[47]

RESULTS

Prevalence and Sociodemographic Correlates

The lifetime prevalence rates of MDD-NSUD, MDD-SUD, and SIDD in the general population were 7.41%, 5.82%, and 0.26%, respectively. Individuals with MDD-SUD were more likely than those with MDD-NSUD to be male, never married, US-born, and 30–44 years old; to have attended college; and to have personal and family incomes ≥ $20,000. Individuals with MDD-SUD were significantly less likely than those with MDD-NSUD to be black, Asian, or Hispanic and 65 years or older; to live in the South; and to have public insurance (Table 1).

Individuals with SIDD were more likely than individuals with MDD-NSUD to be male, less likely to be 65 years or older, and more likely to lack insurance. Individuals with SIDD were more likely than those with MDD-SUD to be black, have at most a high school diploma, and lack insurance. They were less likely than individuals with MDD-SUD to have a family income ≥ $70,000.

Lifetime Risk Factors

Individuals with MDD-SUD were more likely than individuals with MDD-NSUD to endorse family risk factors, including family history of MDD, SUD, and antisocial behavior; childhood risk factors, including parental loss by

Table 1. Prevalence and Sociodemographic Correlates of Individuals With MDD-NSUD, MDD-SUD, and SIDD

	MDD-NSUD (n = 3,308)		MDD-SUD (n = 2,387)		SIDD (n = 106)		MDD-NSUD[a] vs MDD-SUD		MDD-NSUD[a] vs SIDD		MDD-SUD[a] vs SIDD	
Prevalence/Characteristic	%	SE	%	SE	%	SE	OR	95% CI	OR	95% CI	OR	95% CI
Total prevalence	7.4	0.2	5.8	0.2	0.3	0.0	NA		NA		NA	
Sex												
Male	22.7	1.0	45.4	1.3	46.3	5.5	2.8	2.4–3.3	2.9	1.9–4.6	1.0	0.7–1.6
Female	77.3	1.0	54.6	1.3	53.7	5.5	1.0		1.0		1.0	
Race/ethnicity												
White	75.2	1.5	81.9	1.3	67.8	5.1	1.0		1.0		1.0	
Black	9.1	0.7	5.5	0.5	14.5	4.0	0.6	0.5–0.7	1.8	1.0–3.4	3.2	1.7–6.0
Native American	2.5	0.3	3.9	0.6	6.5	4.0	1.4	1.0–2.2	3.0	0.8–11.0	2.1	0.5–8.0
Asian	4.1	0.7	1.4	0.3	1.4	1.2	0.3	0.2–0.5	0.4	0.1–2.1	1.3	0.2–6.9
Hispanic	9.2	1.1	7.4	0.9	9.7	3.1	0.7	0.6–1.0	1.2	0.6–2.3	1.6	0.8–3.3
Nativity												
US-born	87.9	1.3	95.0	0.7	93.7	3.0	2.6	2.0–3.4	2.0	0.8–5.4	0.8	0.3–2.1
Foreign-born	12.1	1.3	5.0	0.7	6.4	3.0	1.0		1.0		1.0	
Age												
18–29 y	18.9	0.9	20.9	1.0	23.2	4.5	1.0		1.0		1.0	
30–44 y	28.5	1.0	38.2	1.2	43.4	5.7	1.2	1.0–1.5	1.2	0.7–2.2	1.0	0.6–1.8
45–64 y	38.0	1.0	36.6	1.3	26.5	5.6	0.9	0.7–1.0	0.6	0.3–1.1	0.7	0.3–1.3
65+ y	14.6	0.7	4.3	0.5	7.0	2.5	0.3	0.2–0.4	0.4	0.2–0.9	1.5	0.6–3.6
Education												
< High school	15.3	0.9	11.0	0.8	20.0	5.1	0.6	0.5–0.8	1.6	0.8–3.2	2.5	1.2–5.2
High school	28.1	1.0	25.3	1.2	33.9	4.9	0.8	0.7–0.9	1.5	0.9–2.4	1.8	1.1–3.0
College	56.6	1.1	63.7	1.4	46.2	5.7	1.0		1.0		1.0	
Individual income, $												
0–19,999	55.4	1.3	43.4	1.4	51.3	5.4	1.0	1.0–1.0	1.0	1.0–1.0	1.0	
20,000–34,999	21.7	1.0	23.7	1.1	18.7	3.8	1.4	1.2–1.7	0.9	0.6–1.6	0.7	0.4–1.1
35,000–64,999	17.6	1.0	24.0	1.2	23.5	5.1	1.7	1.5–2.1	1.4	0.8–2.7	0.8	0.4–1.5
> 70,000	5.3	0.7	9.0	0.8	6.6	2.6	2.1	1.6–2.9	1.3	0.6–3.2	0.6	0.3–1.5
Family income, $												
0–19,999	25.6	1.1	20.2	1.0	31.1	5.3	1.0		1.0		1.0	
20,000–34,999	20.2	1.0	21.4	1.0	19.1	4.0	1.4	1.1–1.6	0.8	0.5–1.5	0.6	0.3–1.1
35,000–64,999	32.1	1.1	31.8	1.1	31.5	5.5	1.3	1.1–1.5	0.8	0.5–1.5	0.6	0.4–1.2
> 70,000	22.2	1.2	26.6	1.2	18.3	4.3	1.5	1.3–1.8	0.7	0.3–1.3	0.5	0.2–0.9
Marital status												
Married	57.9	1.2	54.1	1.3	50.8	5.2	1.0		1.0		1.0	
Widowed/separated/ divorced	24.5	0.9	25.3	1.0	23.7	5.1	1.1	0.9–1.3	1.1	0.6–2.0	1.0	0.6–1.8
Never married	17.7	0.9	20.6	1.1	25.5	5.0	1.3	1.1–1.5	1.7	1.0–2.8	1.3	0.8–2.3
Urbanicity												
Urban	79.0	1.7	78.7	1.8	75.7	5.7	1.0		1.0		1.0	
Rural	21.0	1.7	21.3	1.8	24.3	5.7	1.0	0.9–1.2	1.2	0.7–2.2	1.2	0.7–2.1
Region												
Northeast	19.0	3.3	17.6	2.8	11.6	3.7	0.8	0.7–1.0	0.5	0.2–1.1	0.6	0.3–1.3
Midwest	22.8	3.1	27.0	3.1	23.9	5.3	1.0	0.8–1.3	0.9	0.5–1.6	0.8	0.5–1.5
South	35.9	3.2	30.0	2.9	37.5	6.5	0.7	0.6–0.9	0.9	0.5–1.6	1.2	0.6–2.2
West	22.3	3.3	25.5	3.4	27.1	6.9	1.0		1.0		1.0	
Insurance												
Private	57.4	1.2	65.0	1.2	45.8	6.0	1.0		1.0		1.0	
Public	25.5	1.0	16.4	1.0	19.6	4.1	0.6	0.5–0.7	1.0	0.6–1.7	1.7	1.0–3.0
No insurance	17.1	0.8	18.6	1.1	34.6	6.1	1.0	0.8–1.1	2.5	1.4–4.6	2.6	1.4–4.9

[a]Reference group.
Abbreviations: CI = confidence interval, MDD-NSUD = lifetime major depressive disorder with no lifetime substance use comorbidity, MDD-SUD = lifetime major depressive disorder and lifetime substance use disorder comorbidity, NA = not applicable, OR = odds ratio, SIDD = lifetime substance-induced depressive disorder.

separation and early-onset anxiety disorder; and adulthood risk factors, including low emotional reactivity, divorce, and stressful life events in the previous 12 months (Table 2).

Individuals with SIDD were significantly more likely than individuals with MDD-NSUD to report higher overall family risk factors, family history of SUD and antisocial behavior, and 12-month history of stressful life events and were less likely to report parental loss by death before age 18 (Table 2). Individuals with SIDD were less likely than those with MDD-SUD to report parental loss by death before age 18.

Comorbidity

Individuals with MDD-SUD and individuals with SIDD were significantly more likely than individuals with MDD-NSUD to have any psychiatric disorder, any Axis I diagnosis, any Axis II diagnosis, and nicotine dependence (Table 3). Individuals with MDD-SUD were significantly more likely than individuals with MDD-NSUD to have dysthymia, any anxiety disorder, panic disorder, social anxiety disorder, specific phobia, and obsessive-compulsive, paranoid, schizoid, histrionic, and antisocial personality disorders.

Table 2. Risk Factors for Depression in Individuals With MDD-NSUD, MDD-SUD, and SIDD

	MDD-NSUD (n = 3,308)		MDD-SUD (n = 2,387)		SIDD (n = 106)		MDD-NSUD[a] vs MDD-SUD		MDD-NSUD[a] vs SIDD		MDD-SUD[a] vs SIDD	
MDD Risk Factor	%	SE	%	SE	%	SE	AOR[b]	95% CI	AOR[b]	95% CI	AOR[b]	95% CI
Family risk factors	75.7	1.0	84.5	0.8	86.4	3.4	1.8	1.5–2.1	2.2	1.2–4.0	1.1	0.6–2.1
Family history of MDD	60.7	1.2	64.5	1.2	53.9	5.4	1.2	1.0–1.4	0.8	0.5–1.3	0.7	0.4–1.1
Family history of SUD[c]	47.8	1.0	64.1	1.1	67.8	5.0	2.2	1.9–2.5	2.4	1.5–4.0	1.1	0.7–1.8
Family history of problem behavior	26.2	1.1	38.4	1.3	42.4	5.4	1.7	1.5–2.0	2.0	1.2–3.4	1.2	0.7–1.9
Childhood risk factors	65.9	1.1	71.6	1.1	73.4	5.0	1.4	1.2–1.6	1.3	0.8–2.1	0.9	0.6–1.5
Parental loss by death before 18 y old	9.6	0.6	9.5	0.7	3.2	1.5	1.1	0.9–1.4	0.3	0.1–0.8	0.2	0.1–0.7
Parental loss by separation before 18 y old	28.9	1.0	37.6	1.2	40.8	6.4	1.6	1.3–1.8	1.4	0.8–2.3	0.9	0.5–1.5
Early onset of anxiety disorder before 18 y old	48.7	1.1	51.8	1.3	54.7	5.0	1.2	1.1–1.4	1.3	0.8–2.0	1.1	0.7–1.6
Conduct disorder before 15 y old	1.4	0.3	2.0	0.4	2.9	1.7	1.1	0.5–2.2	1.3	0.5–3.8	1.4	0.4–5.0
Adulthood risk factors	65.3	1.1	72.2	1.2	65.4	5.4	1.3	1.1–1.5	0.9	0.6–1.4	0.7	0.4–1.1
Ever divorced	31.3	1.1	40.6	1.3	35.2	5.8	1.5	1.3–1.8	1.2	0.7–2.1	0.9	0.5–1.6
Low emotional reactivity	18.8	1.0	23.9	1.0	22.2	4.6	1.2	1.0–1.5	1.0	0.6–1.8	0.8	0.5–1.5
Anxious mood	23.6	0.9	22.6	1.0	26.5	4.5	1.0	0.8–1.2	1.2	0.7–2.0	1.3	0.8–2.0
Low self-esteem	21.9	0.9	22.0	1.1	25.4	6.1	1.0	0.9–1.2	1.1	0.6–2.0	1.1	0.6–2.0
History of stressful life events in the last 12 mo	4.3	0.4	7.3	0.7	11.5	3.8	1.7	1.3–2.2	2.6	1.2–5.6	1.4	0.6–3.2

[a]Reference group. [b]Adjusted for sex, race, nativity, age, education, individual income, family income, marital status, and region. [c]Includes family history of alcohol and drug use disorders.

Abbreviations: AOR = adjusted odds ratio, CI = confidence interval, MDD = major depressive disorder, MDD-NSUD = lifetime major depressive disorder with no lifetime substance use comorbidity, MDD-SUD = lifetime major depressive disorder and lifetime substance use disorder comorbidity, SIDD = lifetime substance-induced depressive disorder, SUD = substance use disorder.

Table 3. Lifetime Prevalence of Axis I and Axis II Disorders in Individuals With MDD-NSUD, MDD-SUD, and SIDD

	MDD-NSUD (n = 3,308)		MDD-SUD (n = 2,387)		SIDD (n = 106)		MDD-NSUD[a] vs MDD-SUD		MDD-NSUD[a] vs SIDD		MDD-SUD[a] vs SIDD	
Comorbid Disorder	%	SE	%	SE	%	SE	AOR[b]	95% CI	AOR[b]	95% CI	AOR[b]	95% CI
Any psychiatric disorder[c]	62.8	1.1	79.8	1.0	81.0	4.4	2.3	1.9–2.7	2.5	1.4–4.4	1.0	0.6–1.7
Any Axis I disorder	56.0	1.2	74.1	1.2	76.9	4.8	2.3	2.0–2.7	2.7	1.6–4.6	1.1	0.6–2.0
Alcohol use disorder	0.0	0.0	91.7	0.7	81.0	3.9					0.4	0.2–0.8
Alcohol abuse	0.0	0.0	44.0	1.4	22.1	4.5					0.4	0.2–0.6
Alcohol dependence	0.0	0.0	47.7	1.4	58.8	5.5					1.7	1.1–2.6
Drug use disorder	0.0	0.0	39.2	1.2	58.9	6.5					2.3	1.4–3.9
Drug abuse	0.0	0.0	26.7	1.1	25.3	5.1					0.9	0.5–1.6
Drug dependence	0.0	0.0	12.4	0.9	33.6	6.2					3.6	2.2–5.8
Nicotine dependence	17.2	0.9	46.3	1.3	57.6	6.0	4.1	3.5–4.8	6.5	3.9–11.0	1.5	0.9–2.6
Dysthymia	17.8	0.9	20.7	0.9	6.8	2.7	1.3	1.1–1.5	0.3	0.1–0.8	0.3	0.1–0.7
Any anxiety disorder	38.3	1.2	45.3	1.3	42.4	6.0	1.4	1.2–1.7	1.2	0.7–2.1	0.9	0.6–1.6
Panic disorder	12.3	0.7	17.2	0.9	17.3	4.6	1.6	1.4–2.0	1.5	0.8–2.7	1.0	0.5–2.0
Social anxiety disorder	10.6	0.7	15.6	0.9	11.0	4.0	1.6	1.3–2.0	0.9	0.4–2.3	0.6	0.3–1.5
Specific phobia	18.8	1.0	22.5	1.1	21.9	5.0	1.4	1.1–1.6	1.2	0.6–2.5	1.0	0.5–2.0
Generalized anxiety disorder	14.9	0.8	15.0	0.9	8.0	3.1	1.0	0.8–1.2	0.5	0.2–1.2	0.5	0.2–1.3
Conduct disorder	1.4	0.3	2.0	0.4	2.9	1.7	1.1	0.5–2.2	1.3	0.5–3.8	1.4	0.4–5.0
Pathological gambling	0.4	0.2	1.0	0.2	2.4	1.3	2.3	0.9–6.1	6.2	1.3–29.6	1.6	0.4–7.1
Psychotic disorder	0.7	0.2	0.8	0.2	0.3	0.3	1.2	0.7–2.3	0.3	0.0–2.3	0.4	0.0–3.5
Any personality disorder	25.4	0.9	37.6	1.2	44.0	5.9	1.6	1.3–1.8	1.9	1.2–2.9	1.2	0.8–1.8
Avoidant	6.3	0.5	6.9	0.6	11.9	3.6	1.0	0.7–1.4	1.5	0.7–3.0	1.6	0.8–3.5
Dependent	1.3	0.3	1.1	0.2	0.0	0.0	0.9	0.5–1.5				
Obsessive-compulsive	14.1	0.9	19.4	0.9	22.0	4.4	1.3	1.1–1.6	1.6	0.9–2.7	1.2	0.7–2.0
Paranoid	8.8	0.6	11.5	0.8	21.9	4.6	1.4	1.1–1.8	2.6	1.5–4.6	1.7	0.9–3.0
Schizoid	6.1	0.5	9.2	0.8	10.5	3.6	1.5	1.2–1.9	1.5	0.7–3.1	1.0	0.5–1.9
Histrionic	2.5	0.4	5.0	0.6	15.7	4.4	2.1	1.5–2.9	6.2	2.8–13.8	3.1	1.5–6.7
Antisocial	2.1	0.3	11.7	0.8	16.9	4.7	4.5	3.1–6.7	4.7	2.3–9.6	1.3	0.8–2.4

[a]Reference group. [b]Adjusted for sex, race, nativity, age, education, individual income, family income, marital status, and region. [c]Any psychiatric disorder other than alcohol use disorder, drug use disorder, and MDD.

Abbreviations: AOR = adjusted odds ratio, CI = confidence interval, MDD-NSUD = lifetime major depressive disorder with no lifetime substance use comorbidity, MDD-SUD = lifetime major depressive disorder and lifetime substance use disorder comorbidity, SIDD = lifetime substance-induced depressive disorder.

Individuals with SIDD were less likely than individuals with MDD-NSUD to have dysthymia but more likely to have pathological gambling and paranoid, histrionic, and antisocial personality disorders. Individuals with SIDD were more likely than individuals with MDD-SUD to have alcohol dependence, any drug use disorder, drug dependence, and histrionic personality disorder; however, they were less likely to have alcohol abuse or dysthymia (Table 3).

Clinical Correlates of Depression

Both individuals with MDD-SUD and individuals with SIDD were significantly more likely than those with

Table 4. Prevalence of *DSM-IV* MDD Criteria and Clinical Characteristics Among Individuals With Lifetime MDD-NSUD, MDD-SUD, and SIDD

	MDD-NSUD (n = 3,308)		MDD-SUD (n = 2,387)		SIDD (n = 106)		MDD-NSUD[a] vs MDD-SUD		MDD-NSUD[a] vs SIDD		MDD-SUD[a] vs SIDD	
MDD Clinical Correlate	Mean	SE	Mean	SE	Mean	SE	Wald *F*	*P* Value	Wald *F*	*P* Value	Wald *F*	*P* Value
No. of criteria	7.0	0.0	7.1	0.0	7.3	0.2	9.9	.002	5.7	.02	2.1	.15
Diagnostic criteria	%	SE	%	SE	%	SE	AOR[b]	95% CI	AOR[b]	95% CI	AOR[b]	95% CI
Depressed mood	95.8	0.4	94.0	0.6	85.9	4.6	0.7	0.5–0.9	0.3	0.1–0.5	0.4	0.2–1.0
Loss of interest	86.1	0.8	89.6	0.8	87.0	3.8	1.3	1.0–1.7	1.1	0.6–2.2	0.8	0.4–1.7
Weight loss/weight gain	82.0	0.9	78.7	1.1	84.7	4.2	1.0	0.8–1.2	1.4	0.7–2.8	1.5	0.7–2.9
Insomnia/hypersomnia	76.4	0.9	79.2	1.0	85.9	3.5	1.2	1.0–1.4	2.0	1.1–3.5	1.7	0.9–3.1
Retardation	52.6	1.1	50.9	1.3	57.7	5.2	1.0	0.9–1.1	1.2	0.7–1.9	1.2	0.8–1.9
Fatigue	84.7	0.8	83.5	1.0	80.4	4.3	1.0	0.8–1.2	0.9	0.5–1.5	0.9	0.5–1.6
Feelings of worthlessness	75.7	0.9	79.6	1.1	87.6	3.0	1.2	1.0–1.5	2.0	1.1–3.7	1.7	1.0–3.1
Trouble concentrating	90.1	0.7	91.4	0.7	90.2	3.0	1.1	0.9–1.4	1.0	0.5–2.2	0.9	0.4–1.9
Thoughts of death	54.4	1.1	62.6	1.2	70.2	5.2	1.4	1.2–1.6	1.9	1.2–3.0	1.4	0.8–2.4
Suicide attempt	7.4	0.5	10.7	0.7	16.9	4.5	1.6	1.2–2.0	2.3	1.1–4.8	1.6	0.9–3.2

[a]Reference group. [b]Adjusted for sex, race, nativity, age, education, individual income, family income, marital status, and region.
Abbreviations: AOR = adjusted odds ratio, CI = confidence interval, MDD = major depressive disorder, MDD-NSUD = lifetime major depressive disorder with no lifetime substance use comorbidity, MDD-SUD = lifetime major depressive disorder and lifetime substance use disorder comorbidity, SIDD = lifetime substance-induced depressive disorder.

MDD-NSUD to report a higher number of *DSM-IV* MDD criteria and were more likely to report insomnia/hypersomnia, feelings of worthlessness, thoughts of death, and suicide attempts but were less likely to report depressed mood. Individuals with MDD-SUD were more likely than individuals with MDD-NSUD to report loss of interest (Table 4).

Course and Treatment Utilization

Individuals with MDD-SUD were significantly more likely than individuals with MDD-NSUD to report a younger age at MDD onset and a higher number of MDD episodes, to receive inpatient treatment, and to report use of alcohol and drugs to help relieve depressive symptoms (Table 5). Individuals with SIDD were also more likely than individuals with MDD-NSUD to be treated as inpatients or in the emergency room for their depressive symptoms. They were more likely to use alcohol or drugs but were less likely to use prescribed medication to help relieve depressive symptoms. Individuals with SIDD also had a lower average number of depressive episodes than individuals with MDD-NSUD. Individuals with SIDD reported significantly fewer depressive episodes and later age of remission from SUD than those with MDD-SUD. In comparison to individuals with MDD-SUD, those with SIDD were less likely to report use of prescribed medication for MDD, yet were more likely to use alcohol and drugs to help relieve depressive symptoms and to seek outpatient, inpatient, and emergency room treatment for SUD (Table 5).

DISCUSSION

In a nationally representative sample of US adults, the lifetime prevalence of MDD-NSUD was 7.41%, whereas the lifetime prevalence of MDD-SUD and SIDD was 5.82% and 0.26%, respectively. These findings indicate that the lifetime prevalence of MDD-NSUD and MDD-SUD is relatively high, whereas SIDD is fairly uncommon in the general population. The differences between the low prevalence SIDD estimates in this study and those derived from clinical samples[20,29,48] may be a consequence of help-seeking patterns among individuals with SUD with co-occurring depression and differences in assessment methods. In treatment settings, without information on the longitudinal course of the disorder or use of structured interviews, clinicians may tend to preferentially diagnose patients with SIDD rather than MDD-SUD.[49]

A family history of psychopathology and most childhood and adulthood risk factors were more common in MDD-SUD than in MDD-NSUD. These findings are similar to those of Sher and colleagues,[50] who found that individuals with MDD-AUD were more likely to have a family history of AUD and abuse during childhood than those with MDD and no AUD comorbidity. These results suggest that SUD is a marker for greater severity in individuals with MDD and that some risk factors (eg, family history of psychopathology) may not be disorder-specific but, instead, shared between MDD and SUD.[51–53] The earlier age at MDD onset, higher number of MDD criteria met, higher number of depressive episodes, and higher rates of psychiatric comorbidity found among those with MDD-SUD in this study are consistent with this interpretation. By contrast, there were no significant differences in the prevalence of risk factors between MDD-SUD and SIDD (including family history of depression), other than higher rates of parental loss by death before age 18 among those with MDD-SUD. The death of a loved one has been consistently associated with MDD exacerbation[54–56] due to prolonged bereavement (more than 2 months). Because, in this study, the diagnosis of MDD precluded the diagnosis of SIDD, it was expected to find fewer individuals reporting early parental separation by death in the group with SIDD than in the others.

We found a higher prevalence of psychiatric comorbidity in MDD-SUD than in MDD-NSUD, further suggesting that MDD-SUD is associated with a general vulnerability to psychopathology and to its exacerbation.[57,58] Taken together,

Table 5. Age at Onset, Illness Course, and Treatment Among Individuals With Lifetime MDD-NSUD, MDD-SUD, and SIDD

	MDD-NSUD (n = 3,308)		MDD-SUD (n = 2,387)		SIDD (n = 106)		MDD-NSUD[a] vs MDD-SUD		MDD-NSUD[a] vs SIDD		MDD-SUD[a] vs SIDD	
	Mean	SE	Mean	SE	Mean	SE	Wald *F*	*P* Value	Wald *F*	*P* Value	Wald *F*	*P* Value
MDD												
Age at onset, y	32.1	0.3	28.4	0.3	28.7	1.3	7.5	.008	0.1	.8289	0.4	.5212
No. of MDD episodes	4.3	0.3	5.3	0.4	2.5	0.6	4.2	.045	7.8	.0069	12.6	.0007
Duration of longest episode, wk	92.95	4.47	94.75	5.78	71.29	16.72	3.5	.066	0.5	.5044	2.5	.1166
Duration of MDD, y	7.33	0.24	7.33	0.25	3.03	0.61	3.0	.088	25.8	< .0001	33.0	< .0001
Treatment seeking of MDD	%	SE	%	SE	%	SE	AOR[b]	95% CI	AOR[b]	95% CI	AOR[b]	95% CI
Treated as outpatient	53.7	1.1	54.8	1.3	49.1	6.0	1.0	0.9–1.2	0.9	0.6–1.6	1.0	0.6–1.7
Treated as inpatient	8.9	0.6	10.5	0.7	18.2	4.0	1.3	1.0–1.6	2.5	1.3–4.7	1.8	1.0–3.4
Emergency room admittance	7.5	0.6	8.7	0.7	14.9	4.0	1.3	1.0–1.7	2.4	1.1–5.0	1.6	0.8–3.1
Pharmacologic treatment	44.1	1.2	43.7	1.3	25.8	5.3	1.1	1.0–1.3	0.5	0.3–0.9	0.5	0.3–0.9
	Mean	SE	Mean	SE	Mean	SE	Wald *F*	*P* Value	Wald *F*	*P* Value	Wald *F*	*P* Value
Age at first treatment, y	35.0	0.4	31.7	0.4	32.6	1.6	2.4	.126	1.1	.3079	1.1	.2957
Time from onset to first treatment, y	3.3	0.2	3.5	0.2	3.2	1.0	2.8	.099	0.0	.9476	0.2	.6268
Self-medication	%	SE	%	SE	%	SE	AOR[b]	95% CI	AOR[b]	95% CI	AOR[b]	95% CI
Use of alcohol to help relieve MDD symptoms	5.5	0.5	33.7	1.2	48.5	6.2	7.4	6.0–9.3	12.9	7.5–22.3	1.9	1.1–3.1
Substance use to help relieve MDD symptoms	0.8	0.2	11.2	0.8	27.8	5.1	11.9	6.9–20.5	48.8	20.9–114.2	2.9	1.6–5.5
SUD			Mean	SE	Mean	SE					*T* Score	*P* Value
Age at onset, y			21.7	0.2	20.0	1.3					1.4	.2437
Age at remission, y			29.2	0.3	30.9	1.2					5.6	.0213
Duration of SUD, y			7.7	0.3	8.6	2.0					0.3	.6117
Treatment seeking of SUD			%	SE	%	SE					AOR[b]	95% CI
Treated as outpatient			13.6	0.9	29.3	5.6					2.8	1.6–5.0
Treated as inpatient			10.7	0.8	22.3	5.1					2.3	1.2–4.3
Emergency room admittance			6.1	0.6	14.4	4.4					2.6	1.4–5.0
			Mean	SE	Mean	SE					*T* Score	*P* Value
Duration from onset to first treatment, y			7.4	0.5	6.2	1.6					0.1	.7715

[a]Reference group. [b]Adjusted for sex, race, nativity, age, education, individual income, family income, marital status, insurance, and region.
Abbreviations: AOR = adjusted odds ratio, CI = confidence interval, MDD = major depressive disorder, MDD-NSUD = lifetime major depressive disorder with no lifetime substance use comorbidity, MDD-SUD = lifetime major depressive disorder and lifetime substance use disorder comorbidity, SE = standard error, SIDD = lifetime substance-induced depressive disorder.

our findings suggest that SUD is associated with a greater overall vulnerability to psychopathology and clinical severity in individuals with MDD. By contrast, MDD-SUD and SIDD had more similar patterns of comorbidity and risk factors, indicating that these 2 conditions may share underlying etiologic factors. Longitudinal studies and clinical studies have shown that independent and substance-induced depressive episodes have adverse prognostic implications for SUD and that both diagnoses predict future independent depressive episodes,[2,10,23,25,26] challenging the predictive validity of this distinction. Biological and genetic studies that investigate shared etiologic pathways and pathophysiologic mechanisms between these diagnostic groups may help to determine the utility of preserving this distinction between induced and independent MDD.

Although some research on SIDD has established relationships with antisocial personality disorder[28] and borderline personality disorder,[23] the present study is the first to report of a strong link between SIDD and histrionic personality disorder. We found a 3-fold increased risk of histrionic personality among those with SIDD versus those with MDD-SUD. It is possible that, in some cases, periods of heavy drug/alcohol use causing SIDD episodes may have been related with the impressionistic style and attention-seeking behaviors found in individuals with histrionic personality. Moreover, individuals with SIDD were as likely as individuals with MDD-SUD and more likely than individuals with MDD-NSUD to be treated as inpatients for their depressive symptoms. Given the high rates of comorbidity and suicide attempts found in our study, the high rates of treatment-seeking in individuals with SIDD and MDD-SUD are probably best understood as an indicator of the clinical severity of their depressive syndrome.[59,60] These results underscore the importance of examining the history of psychiatric disorders and suicidal ideation in patients with MDD-SUD and SIDD.

We also found that individuals with MDD-SUD were less likely to receive pharmacologic treatment for depression than those with MDD-NSUD, despite evidence that antidepressants are efficacious for treatment of depressive symptoms and modestly improve SUD.[61–69] This result is in contrast to previous findings in generalized anxiety disorder (GAD) that showed that individuals with GAD-SUD were as likely as those with GAD-NSUD to receive medication for anxiety symptoms.[70] Furthermore, individuals with SIDD were less likely than individuals with MDD-SUD to receive medication. This finding is consistent with prior

reports that recommend 4 weeks of abstinence in patients before the initiation of antidepressant treatments.[63–65,68] However, individuals in our sample reported greater use of substances to relieve their depressive symptoms, suggesting that in the absence of antidepressant treatment some individuals may resort to self-medication. Although some researchers have argued that depressive symptoms in patients with co-occurring MDD and SUD should be treated without delay,[69,71] few studies to date have challenged the established approach of encouraging abstinence and discouraging pharmacotherapy in the treatment of MDD[61,62] and made available an integrated treatment for both MDD and SUD.[72] The use of psychotherapy or medication for the treatment of SUD should be considered in the treatment of individuals with MDD-SUD and SIDD. In a recent study[62] that evaluated the combination of sertraline and naltrexone for the treatment of patients with depression and alcohol dependence in a 14-week double-blind, placebo-controlled trial, patients in the sertraline-naltrexone group combination were more likely than those in the groups that received only naltrexone, only sertraline, or double placebo to achieve abstinence from alcohol and delay relapse to heavy drinking and less likely to be depressed by the end of treatment or report a serious adverse event. Further controlled trials are needed to examine the role of psychotherapy and medication in the treatment of depressive symptoms and their impact on substance use in patients with MDD-SUD and SIDD. At the same time, psychotherapy or medication for the treatment of SUD should be considered in the treatment of individuals with MDD-SUD and SIDD. Decreases in substance use may contribute to improved mood.

This study has several limitations. First, the cross-sectional design of the study limits elucidation of the directionality between the variables associated to the MDD-NSUD, MDD-SUD, and SIDD groups. Second, we limited our definition of MDD, MDD-SUD, and SIDD to those who met criteria for a full major depressive episode syndrome. Future studies should compare the prevalence and characteristics of individuals meeting fewer than 5 *DSM-IV* criteria for MDD. Third, the reliability of the diagnoses of mood and anxiety disorders was fair to good, which may have attenuated the relationship between our variables in the study. Thus, our results are conservative. Fourth, the relatively large number of comparisons in this study may have generated some individual results that were significant by chance. However, the overall pattern of higher severity among those with MDD-SUD in comparison to those with MDD-NSUD is quite consistent and unlikely to be due to chance. Furthermore, the lack of differences between MDD-SUD and SIDD in patterns of comorbidity and risk factors would have been even more marked if a more stringent level of significance had been used, also supporting the similarity between MDD-SUD and SIDD. Fifth, to maximize statistical power and stability of the estimates, we combined alcohol use disorders and drug use disorders and considered SUD as a single unitary entity. Future research is needed to establish whether the effects on MDD of alcohol and specific types of drugs differ.[71]

Despite these limitations, this study provides the most comprehensive information to date on the prevalence, psychiatric comorbidity, risk factors, clinical correlates, and treatment patterns among individuals suffering from MDD with and without comorbid SUD and those with SIDD. The co-occurrence of MDD and SUD is associated with higher overall vulnerability to additional psychopathology, a higher number of depressive episodes, more severe depressive episodes, and higher rates of suicide attempts than MDD-NSUD. SIDD has low prevalence but is associated with high clinical severity, low rates of medication treatment, and high rates of substance use to relieve depressive symptoms. Similar patterns of comorbidity and risk factors in individuals with SIDD and those with MDD-SUD suggest that these disorders may share underlying etiologic factors.

Drug names: naltrexone (Vivitrol, ReVia, and others), sertraline (Zoloft and others).

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